Diet and Atherosclerosis. The article of (48) Dayton and Pearce has provoked some comments from the authors (Lancet 28 February 1970).

DIET AND ATHEROSCLEROSIS

SIR,—The leading article (Nov. 1, p. 919) in which you discussed our trial[1] of a diet high in unsaturated fat made it clear that our report had not dealt adequately with at least one crucial question. Specifically, your article suggested that the low incidence of atherosclerotic events in participants on the experimental diet might have been due to the chance inclusion of a smaller number of heavy cigarette smokers in that group than in the control group. In order to satisfy ourselves and others on this point, we have undertaken further analysis of our results in relation to smoking habits. The results of this analysis, reported below, provide convincing evidence that differences in smoking habits could not have accounted for the favourable experience of subjects on the experimental diet.

We have examined the question by stratifying the subjects on the basis of cigarette-smoking habits as reported at the time of entry into the trial. The outcome experience of the control and experimental groups was then compared within each stratum. Incidence of the primary end-point (ischæmic heart-disease manifested by sudden death or by definite myocardial infarction) was expressed in terms of

1. Dayton, S., Pearce, M. L., Hashimoto, S., Dixon, W. J., Tomiyasu, U. American Heart Association Monograph no. 25. New York, 1969.

TABLE I—NUMBERS AND INCIDENCE-RATES OF MAJOR END-POINTS, STRATIFIED BY CIGARETTE-SMOKING HABITS AT ENTRY INTO THE TRIAL

Cigarette use at entry into study	Control group		Experimental group	
	No. of subjects	Incidence* per 100 man-years	No. of subjects	Incidence* per 100 man-years
Less than 10 cigarettes per day:				
No. of men in subgroup..	166	..	164	..
S.D. or M.I.	25	2·45	21	2·02
S.D., M.I., or C.I.	32	3·13	25	2·40
Any "hard" end-point†	32	3·13	27	2·60
Fatal atherosclerotic events	20	1·95	18	1·73
10–20 cigarettes per day:				
No. of men in subgroup..	129	..	173	..
S.D. or M.I.	22	2·56	20	1·76
S.D., M.I., or C.I.	30	3·49	21	1·85
Any "hard" end-point ..	34	3·95	25	2·20
Fatal atherosclerotic events	26	3·02	19	1·67
More than 20 cigarettes per day:				
No. of men in subgroup..	70	..	45	..
S.D. or M.I.	13	2·66	8	1·70
S.D., M.I., or C.I.	17	3·73	8	2·04
Any "hard" end-point ..	20	4·39	8	2·04
Fatal atherosclerotic events	16	3·51	8	2·04
Not known:				
No. of men in subgroup	57	..	42	..
S.D. or M.I.	5	1·24	6	1·95
S.D., M.I., or C.I.	8	1·99	8	2·60
Any "hard" end-point ..	10	2·48	8	2·60
Fatal atherosclerotic events	8	1·99	5	1·62
All subjects:				
No. of men in group ..	422	..	424	..
S.D. or M.I.	65	2·57	55	1·87
S.D., M.I., or C.I.	87	3·18	60	2·16
Any "hard" end-point..	96	3·51	66	2·38
Fatal atherosclerotic events	70	2·55	48	1·73

* A man with more than one event at the category cited was counted once only.

† Includes those events cited in the preceding footnote, plus the following: interruption of an extremity due to ischæmic gangrene, ruptured aneurysm, arterial infection.

S.D. = sudden death due to ischæmic heart-disease.
M.I. = definite myocardial infarction (overt or silent).
C.I. = definite cerebral infarction.

TABLE II—ESTIMATED "SMOKING-ADJUSTED" INCIDENCE OF MAJOR END-POINTS FOR TOTAL STUDY POPULATION

Clinical incident	Adjusted number of subjects affected		Adjusted incidence per 100 man-years	
	Control	Exper.	Control	Exper.
S.D. or M.I.	65·5	52·1	2·38	1·88
S.D., M.I., or C.I. ..	87·8	60·6	3·20	2·18
Any "hard" end-point ..	96·7	66·1	3·52	2·38
Fatal atherosclerotic events ..	70·8	48·3	2·58	1·74

subjects affected per 100 man-years. Incidence rates were also calculated for major end-points in combination.

As indicated in table I, at any of the three levels of cigarette consumption examined, the incidence of clinical events attributable to atherosclerosis was lower in experimental subjects than in individuals on the control diet. Thus when cigarette consumption is the same, the effect of the experimental diet persists.

Although table I makes it clear that there was a dietary effect, whatever the inequalities of the smoking distribution, it is also desirable to determine whether the surplus of heavy smokers in the control group accounted, *in part*, for the more favourable experience of the experimental group. Toward this end, we have developed estimates of "smoking-adjusted" incidence rates—that is, estimates of the outcome which would have resulted if the subjects of each smoking stratum had been allocated in equal numbers to the control and experimental groups. This was done by multiplying the number of subjects affected in a given cigarette-smoking stratum of the control group by $(x+c)/2c$, in which c = number of control subjects in the stratum and x = number of experimental subjects in the stratum; and by making a corresponding calculation for the experimental group. Resulting figures for all strata were totalled. Figures for total man-years at risk were similarly adjusted before calculating the adjusted incidence-rates. The objective of the calculation is to estimate the answer to this question: if a given stratum of a control group contains $1/2(c+x)$ subjects, whose mean experience is similar to that of the c subjects actually allocated to that subgroup; and if a corresponding experimental subgroup likewise contains $1/2(c+x)$ subjects, with mean experience comparable to that of the x subjects actually observed; and if this is true for all smoking strata, then what is the predicted outcome of such a trial? The resulting estimates, given in table II, are nearly identical to the figures actually observed (bottom of table I), the surplus of heavy smokers in the control group having been fully offset by an even larger surplus of moderate smokers (10–20 cigarettes per day) in the experimental group. We conclude, therefore, that the uneven distribution of cigarette-smoking habits had no net effect whatsoever on the outcome of the trial.

Returning to table I, the outcome in the control group reveals the well-known correlation between cigarette smoking and incidence of atherosclerotic complications. The smoking effect is not apparent, however, in the group on experimental diet; indeed, the experience of heavy-smoking experimental subjects was no worse than that of light-smoking and non-smoking subjects on either diet. Whether this is a true interaction between a dietary effect and smoking habits is difficult to judge with confidence on the basis of these observations. A true interaction of this nature, if confirmed by future work, would have important practical and theoretical implications. However, Leren's secondary-prevention trial[2] did not show evidence of interaction between the smoking effect and the diet effect. The reports of other dietary trials have not, to our knowledge, dealt with this question.

2. Leren, P. *Acta med. scand.* 1966, suppl. no. 466.

In referring to a "rebound" in serum-cholesterol levels on resumption of normal diet by experimental subjects, your article conveys a disturbing misinterpretation of our observations. As indicated in fig. 20 of our report, we tested this question by selecting the 10 experimental subjects and the 11 control subjects who had had the best and most prolonged adherence. During the 8 months before termination of the experimental diet, these two subgroups had nearly identical mean serum-cholesterol concentrations. This must be attributed to chance, since the larger groups from which the sub-samples were drawn displayed lower mean levels among the experimental subjects than among the controls (see fig. 5 of our report). On resumption of the regular diet, the experimental subgroup displayed a prompt serum-cholesterol rise comparable in magnitude to the fall seen at the start of the study. Their levels were now higher than those of the control subgroup. This was surely not a "rebound" phenomenon, but rather an expression of the fact that non-dietary influences had set serum-cholesterol levels higher in these 10 experimental subjects than in the 11 men with whom they were compared.

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